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09/654,499	09/01/2000	Michelle A.J. Palmer	4085-226-27	7006

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EXAMINER
ULM, JOHN D

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1646	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/654,499	Applicant(s) Palmer et al.
	Examiner John Ulm	Art Unit 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-30 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3, 4, 6

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

1) Claims 1 to 30 are pending in the instant application.

2) The instant specification does not comply with 37 C.F.R. § 1.84(U)(1), which states that partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. Figures 10B, 11B, 12B and 13B are each presented on multiple panels which are not properly numbered. For example, each of the nine sheets of drawings which make up Figure 10B should be numbered 10B to 10J, respectively. Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly.

3) The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 02 April of 2001 have been approved.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4) Claims 19 to 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. A critical element of the disclosed invention is the requirement that each member of

a pair of interacting proteins be fused to one member of a pair of complementary β-galactosidase mutants. It is only when both members of that pair of complementary β-galactosidase mutants are brought together through protein-protein interaction that an enzymatic activity is produced. The association of a chimeric protein consisting of β-arrestin fused to a β-galactosidase complementary mutant with a ligand-activated G protein-coupled receptor **will not produce an enzymatic activity** if that G protein-coupled receptor does not contain a complementary form of the β-galactosidase mutant contained in the chimeric β-arrestin. The invention, as claimed, is inoperable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5) Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation "GPCR", and the claim also recites "a β-adrenergic receptor", which is the narrower statement of the range/limitation.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6) Claims 19 to 23 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative for those reasons given above and therefore it lacks utility.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7) Claims 1 to 18 and 24 to 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Blau et al. patent (6,342,345 B1) in view of the Barak et al. patent (5,891,646). The Blau et al. patent described a system for the detection of the molecular interaction between two proteins in an intact cell by expressing each of those proteins as a fusion protein comprising one member of a pair of complementary β-galactosidase mutants. In the first paragraph under "DISCLOSURE OF THE INVENTION", Blau et al. taught "methods and compositions for detecting, assaying and quantitating molecular interactions within living cells and in vitro, through complementation between two or more low affinity reporter subunits" which "enables, for the first time, the study of protein-protein interactions and their control in mammalian cells without reliance upon the transcriptional activation of a reporter gene construct". The following paragraph further taught that "[i]nteractions occurring within the nucleus of the cell, interactions occurring in the cytoplasm, on the cell surface, within or on the surface of organelles, or between cytoplasmic and surface (either cellular or organellar) molecules, as well a[s] interactions occurring outside the cell, are capable of being detected" by employing the method described therein. Example 11 of this patent, as illustrated in Figure 7a, specifically taught the application of the system described therein to the detection of receptor activation. The Blau et al. patent does not anticipate the instant invention only because it does not limit the

method described therein to the detection of the interaction of a G protein-coupled receptor with other proteins such as β-arrestin.

The Barak et al. patent described a method of identifying compounds which act as ligands (abstract), agonists (ln. 53, colm. 2) and antagonists (ln. 12, colm. 3) of a selected G protein-coupled receptor by indirectly measuring the ligand-induced association of that receptor with a fluorescent labeled β-arrestin molecule as indicated by the accumulation of the labeled β-arrestin at the cell surface, where the receptor is located. This patent clearly taught the identification of G protein-coupled receptor agonists and antagonists by detecting the binding of a G protein-coupled receptor to β-arrestin in response to the activation of that receptor by an agonist. An artisan of ordinary skill in the art of molecular biology would have recognized that the method of Barak et al. was limited by the fact that it did not allow detection of the direct interaction of the fluorescent labeled β-arrestin employed therein with a specific G protein-coupled receptor. That artisan would have realized that the fluorescent labeled β-arrestin would have accumulated at the cell membrane in response to the activation of any G protein-coupled receptor which might be present in the cell. This concern was addressed in Example 6 of Barak et al., which demonstrated the colocalization of an antibody-labeled β_2 adrenergic receptor with the fluorescent labeled β-arrestin upon exposure of the cell to the adrenergic receptor agonist isoproterenol. Therefore, that artisan would have appreciated the fact that an accurate measurement of the ligand activation of a particular receptor by employing the method of Barak et al. would require the inclusion of a control consisting of a cell which is otherwise identical to the test cell except for the absence of

the receptor of interest. That artisan would have understood that the method of detecting protein-protein interaction that was described by Blau et al. would not have required such a control because it measured the direct interaction of two specific proteins and, therefore, would allow one to measure the direct interaction of β-arrestin with a specific G protein-coupled receptor in an intact cell irrespective of the interaction of β-arrestin with any other G protein-coupled receptor which might be present in that cell. Therefore, that artisan would have found it *prima facie* obvious to have employed the β-galactosidase complementation system of Blau et al. to detect the interaction of β-arrestin with a particular G protein-coupled receptor to identify agonists and antagonists thereto as taught by Barak et al. because that artisan would have been more confident that the results obtained by the method of Blau et al. were representative of the action of the particular receptor of interest.

Further, because it was well known in the art that the activation of G protein-coupled receptors also involved the dimerization of those receptors as well as their interaction with a plurality of cytoplasmic proteins including G protein complexes and G protein-coupled receptor kinases, an artisan would have found it *prima facie* obvious to have employed the β-galactosidase complementation system of Blau et al. to detect the interaction of any of these proteins with one another in an intact cell in response to receptor activation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800